General

Guideline Title

Preterm labour and birth.

Bibliographic Source(s)

National Collaborating Centre for Women's and Children's Health. Preterm labour and birth. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Nov 20. 24 p. (NICE guideline; no. 25).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation), and are defined at the end of the "Major Recommendations" field.

Information and Support

When giving information and support to women at increased risk of preterm labour, with suspected, diagnosed or established preterm labour, or having a planned preterm birth (and their family members or carers as appropriate):

- Give this information and support as early as possible, taking into account the likelihood of preterm birth and the status of labour
- Follow the principles in the NICE guideline on patient experience in adult NHS services
- Bear in mind that the woman (and her family members or carers) may be particularly anxious
- Give both oral and written information
- Describe the symptoms and signs of preterm labour
- Explain to the woman about the care she may be offered

For women who are having a planned preterm birth or are offered treatment for preterm labour (and their family members or carers as appropriate), provide information and support that includes:

- Information about the likelihood of the baby surviving and other outcomes (including long-term outcomes) and risks for the baby, giving values as natural frequencies (for example, 1 in 100)
- Explaining about the neonatal care of preterm babies, including location of care
- Explaining about the immediate problems that can arise when a baby is born preterm
- Explaining about the possible long-term consequences of prematurity for the baby (how premature babies grow and develop)
- Ongoing opportunities to talk about and state their wishes about resuscitation of the baby
- An opportunity to tour the neonatal unit
- An opportunity to speak to a neonatologist or paediatrician

Prophylactic Vaginal Progesterone and Prophylactic Cervical Cerclage

Offer a choice of either prophylactic vaginal progesterone or prophylactic cervical cerclage to women:

- With a history of spontaneous preterm birth or mid-trimester loss between 16^{+0} and 34^{+0} weeks of pregnancy and
- In whom a transvaginal ultrasound scan has been carried out between 16^{+0} and 24^{+0} weeks of pregnancy that reveals a cervical length of less than 25 mm

Discuss the benefits and risks of prophylactic progesterone and cervical cerclage with the woman and take her preferences into account.

Offer prophylactic vaginal progesterone to women with no history of spontaneous preterm birth or mid-trimester loss in whom a transvaginal ultrasound scan has been carried out between 16^{+0} and 24^{+0} weeks of pregnancy that reveals a cervical length of less than 25 mm.

Consider prophylactic cervical cerclage for women in whom a transvaginal ultrasound scan has been carried out between 16^{+0} and 24^{+0} weeks of pregnancy that reveals a cervical length of less than 25 mm and who have either:

- Had preterm prelabour rupture of membranes (P-PROM) in a previous pregnancy or
- A history of cervical trauma

Diagnosing P-PROM

In a woman reporting symptoms suggestive of P-PROM, offer a speculum examination to look for pooling of amniotic fluid and:

- If pooling of amniotic fluid is observed, do not perform any diagnostic test but offer care consistent with the woman having P-PROM (see "Antenatal Prophylactic Antibiotics for Women with P-PROM," "Identifying Infection in Women with P-PROM," and "Maternal Corticosteroids")
- If pooling of amniotic fluid is not observed, consider performing an insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test of vaginal fluid

If the results of the insulin-like growth factor binding protein-1 or placental alpha-microglobulin-1 test are positive, do not use the test results alone to decide what care to offer the woman, but also take into account her clinical condition, her medical and pregnancy history and gestational age, and either:

- Offer care consistent with the woman having P-PROM (see "Antenatal Prophylactic Antibiotics for Women with P-PROM," "Identifying Infection in women with P-PROM," and "Maternal Corticosteroids") below or
- Re-evaluate the woman's diagnostic status at a later time point

If the results of the insulin-like growth factor binding protein-1 or placental alpha-microglobulin-1 test are negative and no amniotic fluid is observed:

- Do not offer antenatal prophylactic antibiotics
- Explain to the woman that it is unlikely that she has P-PROM, but that she should return if she has any further symptoms suggestive of P-PROM or preterm labour

Do not use nitrazine to diagnose P-PROM.

Do not perform diagnostic tests for P-PROM if labour becomes established in a woman reporting symptoms suggestive of P-PROM.

Antenatal Prophylactic Antibiotics for Women with P-PROM

Offer women with P-PROM oral erythromycin 250 mg 4 times a day[1] for a maximum of 10 days or until the woman is in established labour (whichever is sooner).

For women with P-PROM who cannot tolerate erythromycin or in whom erythromycin is contraindicated, consider oral penicillin for a maximum of 10 days or until the woman is in established labour (whichever is sooner).

Do not offer women with P-PROM co-amoxiclav as prophylaxis for intrauterine infection.

For guidance on the use of intrapartum antibiotics, see the NGC summary of the NICE guideline Antibiotics for early-onset neonatal infection. Antibiotics for the prevention and treatment of early-onset neonatal infection.

Identifying Infection in Women with P-PROM

Use a combination of clinical assessment and tests (C-reactive protein, white blood cell count and measurement of fetal heart rate using cardiotocography) to diagnose intrauterine infection in women with P-PROM.

Do not use any one of the following in isolation to confirm or exclude intrauterine infection in women with P-PROM:

- A single test of C-reactive protein
- White blood cell count
- Measurement of fetal heart rate using cardiotocography

If the results of the clinical assessment or any of the tests are not consistent with each other, continue to observe the woman and consider repeating the tests.

'Rescue' Cervical Cerclage

Do not offer 'rescue' cervical cerclage to women with:

- Signs of infection or
- Active vaginal bleeding or
- Uterine contractions

Consider 'rescue' cervical cerclage for women between 16^{+0} and 27^{+6} weeks of pregnancy with a dilated cervix and exposed, unruptured fetal membranes:

- Take into account gestational age (being aware that the benefits are likely to be greater for earlier gestations) and the extent of cervical dilatation
- Discuss with a consultant obstetrician and consultant paediatrician

Explain to women for whom 'rescue' cervical cerclage is being considered (and their family members or carers as appropriate):

- About the risks of the procedure
- That it aims to delay the birth, and so increase the likelihood of the baby surviving and of reducing serious neonatal morbidity

Diagnosing Preterm Labour for Women with Intact Membranes

Explain to women reporting symptoms of preterm labour who have intact membranes (and their family members or carers as appropriate):

- About the clinical assessment and diagnostic tests that are available
- How the clinical assessment and diagnostic tests are carried out
- What the benefits, risks and possible consequences of the clinical assessment and diagnostic tests are, including the consequences of false positive and false negative test results taking into account gestational age

Offer a clinical assessment to women reporting symptoms of preterm labour who have intact membranes. This should include:

- Clinical history taking
- The observations described for the initial assessment of a woman in labour in the NGC summary of the NICE guideline Intrapartum care: care of healthy women and their babies during childbirth
- A speculum examination (followed by a digital vaginal examination[2] if the extent of cervical dilatation cannot be assessed)

If the clinical assessment suggests that the woman is in suspected preterm labour and she is 29^{+6} weeks pregnant or less, advise treatment for preterm labour.

If the clinical assessment suggests that the woman is in suspected preterm labour and she is 30^{+0} weeks pregnant or more, consider transvaginal ultrasound measurement of cervical length as a diagnostic test to determine likelihood of birth within 48 hours. Act on the results as follows:

- If cervical length is more than 15 mm, explain to the woman that it is unlikely that she is in preterm labour and:
  - Think about alternative diagnoses
  - Discuss with her the benefits and risks of going home compared with continued monitoring and treatment in hospital
  - Advise her that if she does decide to go home, she should return if symptoms suggestive of preterm labour persist or recur
- If cervical length is 15 mm or less, view the woman as being in diagnosed preterm labour and offer treatment as described in "Tocolysis" and "Maternal Corticosteroids" below.

Consider fetal fibronectin testing as a diagnostic test to determine likelihood of birth within 48 hours for women who are 30^{+0} weeks pregnant or more if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable. Act on the results as follows:

- If fetal fibronectin testing is negative (concentration 50 ng/ml or less), explain to the woman that it is unlikely that she is in preterm labour and:
  - Think about alternative diagnoses
  - Discuss with her the benefits and risks of going home compared with continued monitoring and treatment in hospital
  - Advise her that if she does decide to go home, she should return if symptoms suggestive of preterm labour persist or recur
- If fetal fibronectin testing is positive (concentration more than 50 ng/ml), view the woman as being in diagnosed preterm labour and offer treatment as described in "Tocolysis" and "Maternal Corticosteroids" below.

If a woman in suspected preterm labour who is 30^{+0} weeks pregnant or more does not have transvaginal ultrasound measurement of cervical length or fetal fibronectin testing to exclude preterm labour, offer treatment consistent with her being in diagnosed preterm labour (see "Tocolysis" and "Maternal Corticosteroids" below).

Do not use transvaginal ultrasound measurement of cervical length and fetal fibronectin testing in combination to diagnose preterm labour.

Ultrasound scans should be performed by healthcare professionals with training in, and experience of, transvaginal ultrasound measurement of cervical length.

Tocolysis

Take the following factors into account when making a decision about whether to start tocolysis:

- Whether the woman is in suspected or diagnosed preterm labour
- Other clinical features (for example, bleeding or infection) which may suggest that stopping labour is contraindicated
- Gestational age at presentation
- Likely benefit of maternal corticosteroids
- Availability of neonatal care (need for transfer to another unit)
- The preference of the woman

Consider nifedipine for tocolysis[3] for women between 24^{+0} and 25^{+6} weeks of pregnancy who have intact membranes and are in suspected preterm labour.

Offer nifedipine for tocolysis[3] to women between 26^{+0} and 33^{+6} weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour.

If nifedipine is contraindicated, offer oxytocin receptor antagonists for tocolysis.

Do not offer betamimetics for tocolysis.

Maternal Corticosteroids

For women between 23^{+0} and 23^{+6} weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM (see "Diagnosing P-PROM" above), discuss with the woman (and her family members or carers as appropriate) the use of

maternal corticosteroids in the context of her individual circumstances.

Consider maternal corticosteroids for women between 24^{+0} and 25^{+6} weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have P-PROM.

Offer maternal corticosteroids to women between 26^{+0} and 33^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.

Consider maternal corticosteroids for women between 34^{+0} and 35^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM.

When offering or considering maternal corticosteroids, discuss with the woman (and her family members or carers as appropriate):

- How corticosteroids may help
- The potential risks associated with them

Do not routinely offer repeat courses of maternal corticosteroids, but take into account:

- The interval since the end of last course
- Gestational age
- The likelihood of birth within 48 hours

Magnesium Sulfate for Neuroprotection

Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24^{+0} and 29^{+6} weeks of pregnancy who are:

- In established preterm labour or
- Having a planned preterm birth within 24 hours

Consider intravenous magnesium sulfate for neuroprotection of the baby for women between 30^{+0} and 33^{+6} weeks of pregnancy who are:

- In established preterm labour or
- Having a planned preterm birth within 24 hours

Give a 4 g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours (whichever is sooner).

For women on magnesium sulfate, monitor for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon (for example, patellar) reflexes.

If a woman has or develops oliguria or other signs of renal failure:

- Monitor more frequently for magnesium toxicity
- Think about reducing the dose of magnesium sulfate

Fetal Monitoring

Monitoring Options: Cardiotocography and Intermittent Auscultation

Discuss with women in suspected, diagnosed or established preterm labour (and their family members or carers as appropriate):

- The purpose of fetal monitoring and what it involves
- The clinical decisions it informs at different gestational ages
- If appropriate, the option not to monitor the fetal heart rate (for example, at the threshold of viability)

Involve a senior obstetrician in discussions about whether and how to monitor the fetal heart rate for women who are between 23^{+0} and 25^{+6} weeks pregnant.

Explain the different fetal monitoring options to the woman (and her family members or carers as appropriate), being aware that:

- There is limited evidence about the usefulness of specific features to suggest hypoxia or acidosis in preterm babies

- The available evidence is broadly consistent with that for babies born at term (see "Monitoring during Labour" in the NGC summary of the NICE guideline Intrapartum care: care of healthy women and their babies during childbirth)
- A normal cardiotocography trace is reassuring and indicates that the baby is coping well with labour, but an abnormal trace does not necessarily indicate that fetal hypoxia or acidosis is present

Explain to the woman (and her family members or carers as appropriate) that there is an absence of evidence that using cardiotocography improves the outcomes of preterm labour for the woman or the baby compared with intermittent auscultation.

Offer women in established preterm labour but with no other risk factors (see "Monitoring during Labour" in the NGC summary of the NICE guideline Intrapartum care: care of healthy women and their babies during childbirth) a choice of fetal heart rate monitoring using either:

- Cardiotocography using external ultrasound or
- Intermittent auscultation

For guidance on using intermittent auscultation for fetal heart rate monitoring, see "Monitoring during Labour" in the NGC summary of the NICE guideline Intrapartum care: care of healthy women and their babies during childbirth.

Fetal Scalp Electrode

Do not use a fetal scalp electrode for fetal heart rate monitoring if the woman is less than 34^{+0} weeks pregnant unless all of the following apply:

- It is not possible to monitor the fetal heart rate using either external cardiotocography or intermittent auscultation
- It has been discussed with a senior obstetrician
- The benefits are likely to outweigh the potential risks
- The alternatives (immediate birth, intermittent ultrasound and no monitoring) have been discussed with the woman and are unacceptable to her

Discuss with the woman (and her family members or carers as appropriate) the possible use of a fetal scalp electrode between 34^{+0} and 36^{+6} weeks of pregnancy if it is not possible to monitor the fetal heart rate using either external cardiotocography or intermittent auscultation.

Fetal Blood Sampling

Do not carry out fetal blood sampling if the woman is less than 34^{+0} weeks pregnant.

Discuss with the woman the possible use of fetal blood sampling between 34^{+0} and 36^{+6} weeks of pregnancy if the benefits are likely to outweigh the potential risks.

When offering fetal blood sampling, discuss this with the woman (as described in "Fetal Blood Sampling" in the NGC summary of the NICE guideline Intrapartum care: care of healthy women and their babies during childbirth), and advise her that if a blood sample cannot be obtained a caesarean section is likely.

Mode of Birth

Discuss the general benefits and risks of caesarean section and vaginal birth with women in suspected, diagnosed or established preterm labour and women with P-PROM (and their family members or carers as appropriate) – see "Planning Mode of Birth" in the NGC summary of the NICE guideline Caesarean section.

Explain to women in suspected, diagnosed or established preterm labour and women with P-PROM about the benefits and risks of caesarean section that are specific to gestational age. In particular, highlight the difficulties associated with performing a caesarean section for a preterm birth, especially the increased likelihood of a vertical uterine incision and the implications of this for future pregnancies.

Explain to women in suspected, diagnosed or established preterm labour that there are no known benefits or harms for the baby from caesarean section, but the evidence is very limited.

Consider caesarean section for women presenting in suspected, diagnosed or established preterm labour between 26^{+0} and 36^{+6} weeks of pregnancy with breech presentation.

Timing of Cord Clamping for Preterm Babies (Born Vaginally or by Caesarean Section)

If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding:

- Consider milking the cord and
- Clamp the cord as soon as possible

Wait at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm babies if the mother and baby are stable.

Position the baby at or below the level of the placenta before clamping the cord.

Footnotes

[1]At the time of publication (November 2015), erythromycin did not have a UK marketing authorisation for use in pregnancy. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The summaries of product characteristics for oral erythromycin recommend different dosages. The evidence reviewed for the guideline supports a dosage of 250 mg 4 times a day for prophylaxis in women with P-PROM.

[2]Be aware that if a swab for fetal fibronectin testing is anticipated, the swab should be taken before any digital vaginal examination.

[3]Although this use is common in UK clinical practice, at the time of publication (November 2015), nifedipine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The suggested dosage of nifedipine (as specified in the BNF) is a loading dose of 20 mg orally, followed by 10–20 mg 3 to 4 times daily adjusted according to uterine activity.

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the GDG uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

The following clinical algorithms are available in the full version of the guideline document (see the "Availability of Companion" Documents" field):

- Preventive care
- Diagnosis of preterm labour (PTL)
- Diagnosis of P-PROM
- Care for PTL or P-PROM

In addition, a National Institute for Health and Care Excellence (NICE) pathway titled "Preterm labour and birth overview" is available on the NICE Web site.

Scope

Disease/Condition(s)

- Preterm labour and birth
- Preterm prelabour rupture of membranes (P-PROM)

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Nursing

Obstetrics and Gynecology

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To review the evidence for the care of women who present with signs and symptoms of preterm labour and those who are scheduled to have a preterm birth

Target Population

- Pregnant women who are considered to be at risk of preterm labour and birth because they have a history of:
  - Spontaneous preterm birth
  - Preterm pre-labour rupture of membranes
  - Mid-trimester loss
  - Cervical trauma (including surgery - for example, previous cone biopsy [cold knife or laser], large loop excision of the transformation zone [LLETZ] - any number - and radical diathermy)
- Pregnant women who are considered to be at risk of preterm labour and birth because they have a short cervix that has been identified on ultrasound scan and/or bulging membranes in the current pregnancy

- Pregnant women with preterm pre-labour rupture of membranes
- Women diagnosed to be in spontaneous preterm labour
- Women having planned preterm birth

Note: This guideline does not cover women in labour at term or women with a multiple pregnancy.

Interventions and Practices Considered

1. Providing information and support to women at increased risk of preterm labour and to women who are having a planned preterm birth or are offered treatment for preterm labour
2. Prophylactic vaginal progesterone
3. Prophylactic cervical cerclage
4. Diagnosing preterm prelabour rupture of membranes (P-PROM)
    - Speculum examination
    - Insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test of vaginal fluid
5. Antenatal prophylactic antibiotics for women with P-PROM (oral erythromycin, penicillin)
6. Identifying infection in women with P-PROM
    - Clinical assessment
    - Tests for C-reactive protein
    - White blood cell count
    - Measurement of fetal heart rate using cardiotocography
7. 'Rescue' cervical cerclage when appropriate
8. Diagnosing preterm labour for women with intact membranes
    - Clinical assessment
    - Transvaginal ultrasound measurement of cervical length
    - Fetal fibronectin testing
9. Tocolysis
    - Nifedipine
    - Oxytocin receptor antagonists
    - Betamimetics (not recommended)
10. Maternal corticosteroids
11. Intravenous magnesium sulfate for neuroprotection of the baby
12. Fetal monitoring using cardiotocography, intermittent auscultation, fetal scalp electrodes, or fetal blood sampling
13. Decision making concerning mode of birth (discussing risks and benefits of caesarean section and vaginal birth)
14. Timing of cord clamping for preterm babies (born vaginally or by caesarean section)

Major Outcomes Considered

- Neonatal outcomes
    - Perinatal mortality
    - Birth trauma
    - Timing of birth in relation to timing of intervention
    - Admission to neonatal intensive care for respiratory support
    - Need for mechanical ventilation
    - Hypoxic ischaemic encephalopathy
    - Respiratory disorders
    - Intraventricular haemorrhage
    - Sepsis
    - Length of stay in neonatal intensive care/special baby unit
    - Chronic lung disease
    - Long-term infant mortality
    - Developmental delay
- Maternal outcomes
    - Maternal mortality

    - Pharmacological adverse effects
    - Surgical adverse events
    - Mode of birth
    - Physical birth trauma
    - Sepsis
    - Women's experience of labour and birth
    - Psychological birth trauma
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were framed according to the type of question:

- Intervention – PICO (patient, intervention, comparison and outcome)
- Diagnostic test accuracy – population, index tests, reference standard and target condition for reviews of diagnostic test accuracy
- Qualitative – population, area of interest, outcomes

These frameworks guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the committee. The review questions were drafted by the NCC-WCH technical team and were refined and validated by the committee. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full guideline appendices [see the "Availability of Companion Documents" field]).

A total of 18 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions. See Table 1 in the full version of the guideline.

Searching for Evidence

Clinical Literature Search

During the scoping stage, a search was conducted for guidelines and reports on Web sites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead of print or 'online early' publications were not routinely undertaken.

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2012 (see the "Availability of Companion Documents" field).

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in Medline, EMBASE and The Cochrane Library. All searches were updated in March 2015 with the exception of the

search for the review question that included the network meta-analysis (NMA) which was last updated in January 2015. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

Search strategies were quality assured by cross checking reference lists of highly relevant papers, analysing search strategies in systematic reviews (SRs) and asking the committee members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix E in the full guideline appendices.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria specified in the protocols (see Appendix D in the full guideline appendices).

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to preterm labour in the National Health Service Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED) and Health Technology Assessment (HTA) databases with no date restrictions. Additionally, the search was run on Medline and EMBASE, using a specific economic filter, from 2011 to ensure recent publications that had not yet been indexed by the economic databases were identified. This was supplemented by additional searches that looked for economic papers specifically relating to gas exchange management as this was an area identified for original economic modelling. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The search strategies for the health economic literature search are included in Appendix E of the full version of the guideline document. All searches were updated in March 2015. No papers published after this date were considered.

Evidence of Effectiveness

The evidence was reviewed following these steps:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix D in the full guideline appendices).

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix D in the full guideline appendices. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix G in the full guideline appendices. The committee was consulted about any uncertainty regarding inclusion or exclusion.

Evidence of Cost-effectiveness

The committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought, a systematic review of the published economic literature was undertaken and a new cost effectiveness analysis was conducted in priority areas.

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts and full papers were then obtained
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered for inclusion as economic evidence.

Number of Source Documents

See Appendix F: PRISMA Flow Diagrams in the full guideline appendices (see the "Availability of Companion Documents" field) for results of literature searches and number of included studies for each of the guideline topics. See Appendix G for a list of excluded studies and reasons for exclusion.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Evidence of Effectiveness

The evidence was reviewed following these steps:

- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual 2012 (see the "Availability of Companion Documents" field). For diagnostic questions the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist was followed.
- Key information was extracted on the study's methods, patient, intervention, comparison, outcome (PICO) factors and results. These were presented in summary tables in each chapter and evidence tables (in Appendix H in the full guideline appendices [see the "Availability of Companion Documents" field]).
- Summaries of evidence were generated by outcome and were presented in committee meetings:
    - Randomised studies – data were meta-analysed where appropriate and reported in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for interventional reviews)
    - Diagnostic/predictive accuracy studies – presented as measures of diagnostic/predictive test accuracy (sensitivity, specificity, positive and negative predictive value); a meta-analysis was only conducted when the included studies were not heterogeneous

    - Qualitative studies – the themes of the studies were organised in a modified version of a GRADE profile, where possible, along with quality assessment otherwise presented in a narrative form
- Of all data extracted, 50% was quality assured by a second reviewer and 50% of the GRADE quality assessment was quality assured by a second reviewer to minimise any potential risk of reviewer bias or error.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software or STATA. Fixed-effects (Mantel–Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes.

For the continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (probability [p] values or 95% CIs) if available: metaâ€analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects or as a narrative summary. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for this evidence and this has been recorded in the footnotes of the GRADE tables. When more than 2 studies reported a continuous outcome, the presentation of mean (SD) per comparison group was taken by averaging the means of included studies.

In instances where multiple scales were reported for a single outcome, mean differences were standardised (divided by their SD) before pooling, giving meta-analysed results that were reported as standardised mean differences (SMD), with a standard deviation of 1.

Where reported, time-to-event data were presented as a hazard ratio or results from a Cox hazard proportion model were given as a result from a multivariate analysis.

Statistical heterogeneity was assessed by visually examining the forest plots and by considering the chi-squared test for significance at p less than 0.1 or an I-squared inconsistency statistic (with an I-squared value of 50%–74.99% indicating serious inconsistency and I-squared value of over 75% indicating very serious inconsistency). If the heterogeneity still remained, a random effects model was employed to provide a more conservative estimate of the effect. Where considerable heterogeneity was present, the authors set out to perform predefined subgroup analyses based on the following factors:

- Different gestational age of fetus
- Inclusion of studies with mixed populations of women with single and multiple pregnancies
- Different groups of women at high risk of preterm labour

Data Synthesis for Diagnostic Test Accuracy Review

For diagnostic test accuracy studies, the outcomes reported were sensitivity, specificity, positive likelihood ratio and negative likelihood ratio.

The assessment of usefulness of the diagnostic or predictive accuracy of tests followed the terms and thresholds below:

Sensitivity and specificity:

- High – 90% and above
- Moderate – 75% to 89.9%
- Low – 74.9% or below

Positive likelihood ratio:

- Very useful – more than 10
- Moderately useful – 5 to 10
- Not useful – less than 5

Negative likelihood ratio:

- Very useful – 0 to 0.1
- Moderately useful – more than 0.1 to 0.5
- Not useful – more than 0.5

Data Synthesis for Qualitative Review

For the qualitative review in the guideline, results were presented in 2 ways:

- NICE checklists on assessing qualitative studies were used to assess the quality assessment of individual studies
- Results were reported narratively by individual study when appropriate

Data Synthesis Using a Network Meta-analysis

A network meta-analysis (NMA) was formulated to synthesise direct and indirect evidence of treatments' efficacy to determine which treatments are most effective at delaying preterm birth to improve the outcomes for the baby with least harm to, and least adverse effects for, the woman while preserving randomisation within primary studies for the outcomes of:

- Neonatal mortality
- Perinatal mortality
- Respiratory distress syndrome (RDS)
- Intraventricular haemorrhage (IVH)
- Adverse events requiring discontinuation of treatment
- Delay of birth by at least 48 hours
- Neonatal sepsis
- Gestational age at birth

Hierarchical Bayesian NMAs were performed using the software WinBUGS version 1.4. These models were based on original work from the University of Bristol (https://www.bris.ac.uk/cobm/research/mpes/mtc.html).

A class effect model was adopted for the new NMA because it was hypothesised that treatments within class would borrow similar clinical characteristics and mechanisms of effect. In other words, results for one member of the class in relation to efficacy and side effects were considered to be generalisable to other members of that same class. Since there was no evidence of within-class variability for any of the outcomes considered, all the results presented assume that all treatments in a class have the same relative effect (see Appendix J in the full guideline appendices).

Trials with non-UK licensed interventions were included in the NMA to allow the maximum use of available evidence and borrow strength of loops in the network only if there was at least 1 trial that included licensed (for preterm labour or for other conditions) interventions for the same class. Some other considerations in the design of the NMA were:

- The committee discussed that although dosage, mode of administration and timing of treatment may influence the effectiveness of different tocolytics interventions, it was considered unlikely for this factor to change the direction of relative effect for the different interventions tested in the analysis. The committee therefore decided not to consider any confounding effect of these factors in the NMA.
- Some of the included studies examined drugs that are not licensed as tocolytics for use in pregnancy (including nylidrin and barusiban). These drugs were included in the NMA to increase the size of the network and because it is not uncommon for drugs that are not licenced for pregnancy indications to be prescribed for use in this context.
- The committee chose to have separate classes for alcohol/ethanol and combination treatments (classed as 'other') in the new NMA.

Standard deviations (SDs) were imputed where they were not reported for 5 studies assessing estimated gestational age. Imputed values were based on the median SD for each of these treatments from other included studies. A sensitivity analysis using the upper quartile of the reported SD was carried out. Apart from increased uncertainty in estimates the main results were not affected.

Assessment of Consistency

Consistency was assessed by checking the agreement of direct and indirect evidence using a node-split model. Bayesian p values for agreement between direct and indirect evidence were calculated. When these were lower than 0.05, included trials were inspected to help determine reasons for the potential inconsistency, bearing in mind that multiple probabilities of disagreement are being calculated and there is the potential to find spurious results.

Consistency was considered as part of the quality appraisal of the evidence for the NMA (see below).

Model Evaluation

For all the networks set up in the NMA, models for fixed and random effects were developed and then these were compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. However, if the difference in DIC between a fixed and random effect model was less than 5 points, and the models make very similar inferences, then reviewers would report the results from a fixed effects model as it does not make as many assumptions as the random effect model and contains fewer parameters, and it is easier for clinical interpretation than the random effects model.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included randomised controlled trials (RCTs) and, where appropriate, observational studies was evaluated and presented using an adaptation of the GRADE toolbox developed by the international GRADE working group. The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results and clinical evidence profile tables were generated. The clinical evidence profile table includes details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 in the full version of the guideline. Each element was graded using the quality levels listed in Table 3 in the full version of the guideline.

The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (see Table 2 in the full version of the guideline).

The GRADE toolbox is currently designed only for randomised trials and observational studies but the working group adapted the quality assessment elements and outcome presentation for diagnostic accuracy and prognostic studies subject to data availability.

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

- A quality rating was assigned based on the study design. RCTs start as high, observational studies as moderate and uncontrolled case series as low or very low.
- The rating was then downgraded for the specified criteria: risk of bias (study limitations); inconsistency; indirectness; imprecision; and publication bias. These criteria are detailed in Sections 2.2.6.2 to 2.2.6.6 of the full version of the guideline. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was a large magnitude of effect or a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
- The downgraded/upgraded ratings were then summed and the overall quality rating was revised. For example, all RCTs started as high and the overall quality became moderate, low or very low if 1, 2 or 3 points were deducted respectively.
- The reasons or criteria used for downgrading were specified in the footnotes.

Diagnostic Studies

For diagnostic accuracy studies, the QUADAS version 2 (QUADASâ€2) checklist was used (see Appendix F in The guidelines manual 2012 [see the "Availability of Companion Documents" field]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADASâ€2 consists of 4 domains (see Figure 1 in the full version of the guideline):

- Patient selection
- Index test
- Reference standard
- Flow and timing

Quality Assessment of NMA

The quality of evidence from NMA was assessed using a modified GRADE appraisal process.

Risk of bias was assessed using the quality assessment undertaken by Haas 2012 and for all additional studies using the checklist developed by the Technical Support Unit (TSU) commissioned by NICE.

Indirectness was assessed using information about the study population and imprecision based on credible intervals in line with standard GRADE methodology. Inconsistency was assessed by comparing estimates based on direct and indirect data included in the network. Where there was evidence of inconsistency (see Appendix J in the full guideline appendices) then quality was downgraded. Imprecision was assessed based on the credible interval within each comparison. Data were downgraded if a credible interval crossed the two default MIDs or majority of the comparisons.

Assessing Clinical Importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by comparison (for intervention reviews) or by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome
- A brief description of the participants
- An indication of the direction of effect (if a particular treatment is beneficial or harmful compared with the other, or whether there is no difference between the 2 tested treatments)
- A description of the overall quality of evidence (GRADE overall quality)

Evidence of Cost-effectiveness

The committee is required to make decisions based on the best available evidence of both clinical and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought, a systematic review of the published economic literature was undertaken and a new cost-effectiveness analysis was conducted in priority areas.

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the guidelines manual
- Extracted key information about study methods and results into evidence tables (included in Appendix H in the full guideline appendices)
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question in the full version of the guideline)

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality for each economic evaluation. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual 2012. It also shows the incremental costs, incremental effects (for example quality-adjusted life years [QALYs]) and the incremental cost-effectiveness ratio for the base-case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 in the full version of the guideline for more details.

Methods Used to Formulate the Recommendations

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Who Developed This Guideline?

A multidisciplinary Guideline Committee comprising healthcare professionals, researchers and lay members developed this guideline.

NICE funds the NCC-WCH and thus supported the development of this guideline. The committee was convened by the NCC-WCH in accordance with guidance from NICE.

The committee met every 4 to 6 weeks during the development of the guideline. Staff from the NCC-WCH provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

Developing Recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature (all evidence tables are in Appendix H in the full guideline appendices [see the "Availability of Companion Documents" field])
- Summary of clinical and economic evidence and quality assessment (as presented in Chapters 3 to 15 in the full version of the guideline)
- Forest plots (see Appendix I in the full guideline appendices)
- A description of the methods and results of the cost effectiveness analysis undertaken for the guideline (see Chapter 16 in the full version of the guideline)

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the prioritised outcomes and taking into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the committee's values and preferences) and the confidence the committee had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

In areas where no substantial clinical research evidence was identified, the committee considered other NICE relevant guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of National Health Services (NHS) resources (interventions) was considered was based on committee consensus in relation to the likely cost effectiveness implications of the recommendations. The committee also identified areas where evidence to answer their review questions was lacking and used this information to formulate recommendations for future research. When clinical and economic evidence was of poor quality, conflicting or absent, the committee members drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues.

The wording of recommendations was agreed by the committee and focused on the following factors:

- The actions healthcare professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions

The main considerations specific to each recommendation are outlined in the "Evidence to recommendations" sections within each chapter of the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The Guideline Committee usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The Guideline Committee uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the Guideline Committee is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The Guideline Committee uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each most review questions, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the committee after formation of the review questions and consideration of the available health economic evidence.

Cost-effectiveness Criteria

The National Institute for Health and Care Excellence's (NICE's) report Social value judgements: principles for the development of NICE guidance (see the "Availability of Companion Documents" field) sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies)
- The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter of the full version of the guideline with reference to issues regarding the plausibility of the estimate or to the factors set out in Social value judgements: principles for the development of NICE guidance.

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless a particular strategy dominates the others with respect to every relevant health outcome and cost.

In the Absence of Economic Evidence

When no relevant published studies were found and a new analysis was not prioritised, the committee made a qualitative judgement about cost-

effectiveness by considering expected differences in resource use between options and relevant UK National Health Service (NHS) unit costs alongside the results of the clinical review of effectiveness evidence.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Validation Process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site when the pre-publication check of the full guideline occurs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Type of Studies

Systematic reviews (SRs) with or without meta-analyses were considered the highest quality evidence to be selected for inclusion. Individual patient data (IPD) meta-analyses are considered the gold standard type of meta-analysis and were prioritised for inclusion in the evidence base of this guideline when appropriate.

Randomised trials and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Literature reviews, posters, letters, editorials, comment articles, conference abstracts, unpublished studies and studies not in English were excluded.

For intervention reviews in this guideline, randomised controlled trials (RCTs) were included because they are considered the most robust study design for unbiased estimation of intervention effects.

If the committee believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised comparative studies were included. For diagnostic reviews, cross-sectional, retrospective studies and case series were included. Please refer to Appendix D in the full guideline appendices (see the "Availability of Companion Documents" field) for full details on the study design of studies selected for each review question.

The committee defined primary outcomes as women's and babies' mortality and birth within 48 hours and within 7 days; and secondary outcomes as long-term infant neurodevelopmental outcomes, birth events (mode of birth, complications of birth, perineal the trauma), newborn events (condition at birth, birth injuries, admission to neonatal units) and women's assessment of birth experience. The committee considered other outcomes when they were relevant to specific questions.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Optimal diagnosis of preterm birth can facilitate transfer to a place where appropriate neonatal intensive care can be provided, a strategy known to improve rates of survival for the baby.
- Although antibiotics given to mothers with preterm prelabour rupture of membranes (P-PROM) seem to have little effect on the long-term health outcomes of children, the short-term advantages (reducing neonatal infection and delaying birth) are such that the committee decided

that antibiotics should be offered routinely to all women with P-PROM.
- There was consistent evidence from randomised trials that maternal corticosteroids are beneficial from 26 weeks' gestation in terms of reducing neonatal morbidity including intraventricular haemorrhage (IVH, all grades and grade III or IV), need for mechanical ventilation and neonatal sepsis.

Refer to the "Consideration of clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for benefits of specific intervention.

Potential Harms

- The evidence base suggested that there may be an increase in maternal adverse effects in women who received prophylactic cerclage compared with those who did not. The Guideline Committee did note, however, that it was not possible to distinguish the nature of the individual adverse effect and thus it was hard to determine the clinical significance of this result. However, they discussed in depth the associated risks for the pregnancy from this technique, such as uterine contractions, bleeding or infection which may lead to miscarriage or preterm labour. These risks were balanced against the benefit from mechanical support to the cervix. The only available data on specific adverse events was for pyrexia which was analysed separately. The results did show a significant increase in the risk of experiencing pyrexia in the group that received prophylactic cerclage compared with the group that received no treatment. However, there was still some uncertainty as to the clinical significance of this result given that none of the trials specified whether the women who had pyrexia had also received antibiotics.
- Potential for adverse drug reactions from prophylactic antibiotics, tocolytics, and magnesium sulfate

Refer to the "Consideration of clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for harms of specific interventions.

Contraindications

Contraindications

The guideline committee recognised that the clinical decision to start tocolytic treatment needs to take into consideration a range of maternal factors such as the woman's status in the care pathway (whether in suspected or diagnosed preterm labour) and the coexistence of other features such as bleeding and infection, in which circumstances delaying preterm labour would be contraindicated.

Qualifying Statements

Qualifying Statements

- Healthcare professionals are expected to take the National Institute for Health and Care Excellence (NICE) clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.
- Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.
- The National Collaborating Centre for Women and Children's Health (NCC-WCH) disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

Implementation: Getting Started

This section of the guideline highlights 2 areas of the preterm labour and birth guideline that could have a big impact on practice and be challenging to implement, along with the reasons why the authors are proposing change in these areas (given in the box at the start of each area). The section also gives information on resources to help with implementation.

The Challenge: Diagnosing Preterm Labour for Women with Intact Membranes

The evidence reviewed for the guideline indicated that transvaginal ultrasound measurement of cervical length is the best diagnostic test for determining the likelihood of birth within 48 hours for women who are 30^{+0} weeks pregnant or more with intact membranes who, after clinical assessment, are in suspected preterm labour. Many women thought to be in preterm labour on clinical assessment will not have a preterm birth. Optimal diagnosis in women with symptoms of preterm labour ensures that preterm labour can be correctly identified and the appropriate clinical management started.

If transvaginal ultrasound measurement of cervical length is not available or not acceptable, fetal fibronectin testing should be considered for ruling out preterm birth within 48 hours. This test is useful, although it is not as good a diagnostic tool as ultrasound measurement of cervical length. Fetal fibronectin testing is a simple test that can be carried out by healthcare professionals very quickly.

Increasing Availability of Transvaginal Ultrasound

Using transvaginal ultrasound measurement of cervical length is not part of routine antenatal care, so implementation is likely to lead to an increase in the number of scans needed. Ensuring that women have access to this diagnostic test may be challenging because of a lack of available specialist equipment and/or expertise, and investment in technology and training may be needed. Staff training will be important to ensure that transvaginal ultrasound measurements of cervical length are performed using consistent and standard criteria.

The National Institute for Health and Care Excellence (NICE) is working with the Royal College of Obstetricians and Gynaecologists (RCOG) to ensure that measuring cervical length using transvaginal ultrasound is included in the ultrasound module for obstetric trainees.

To increase availability, commissioners could:

- Invest in additional ultrasound equipment, ensuring that images can be stored for audit
- Commission a service that is able to provide cervical length scans outside normal working hours. This may be provided by on-call imaging services and/or by training healthcare professionals in obstetric units so that sufficient expertise is available at all times.
- Use the NICE resource impact assessment to work out the cost implications

Promoting the Use of Fetal Fibronectin Testing

When transvaginal ultrasound measurement of cervical length is not available, it is not currently routine practice to use fetal fibronectin testing as a diagnostic test for determining likelihood of birth within 48 hours for women who are 30^{+0} weeks pregnant or more and in suspected preterm labour.

What can obstetric units do to help?

- Raise awareness of when fetal fibronectin testing should be used and that it is a simple test that can be carried out in 5 minutes by healthcare professionals.

The Challenge: Using Tocolysis

Giving an effective tocolytic medicine to women with intact membranes who are in suspected or diagnosed preterm labour can delay the birth. This in turn can improve neonatal outcomes.

Promoting the Use of Tocolysis

Clinical practice varies in terms of which women in preterm labour are offered a tocolytic medicine, when it should be given and the choice of tocolytic. The decision to offer tocolysis should take into account whether neonatal care is available on-site or whether transfer to another hospital will be needed.

To overcome this, the lead clinician for each obstetric unit could:

- Update local guidelines on managing preterm labour with regard to which women should be offered tocolytic medicines, and which

tocolytics are first-line treatment
- Use the NICE baseline assessment tool to determine current prescribing practice
- Use bulletins to raise awareness of these recommendations

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Collaborating Centre for Women's and Children's Health. Preterm labour and birth. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Nov 20. 24 p. (NICE guideline; no. 25).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Nov 20

Guideline Developer(s)

National Guideline Alliance - National Government Agency [Non-U.S.]

Source(s) of Funding

The National Institute for Health and Care Excellence (NICE) funds the National Collaborating Centre for Women and Children's Health (NCC-WCH) and thus supported the development of this guideline.

Guideline Committee

Guideline Committee

Composition of Group That Authored the Guideline

Guideline Committee Members: Judi Barratt, Clinical midwife specialist, Worcester Royal Hospital; Paul Eunson, Consultant Paediatric Neurologist & Honorary Senior Lecturer, Royal Hospital for Sick Children, Edinburgh; Jane Hawdon, Consultant Neonatologist, Barts Health NHS Trust; Jane Norman (*Chair*), Professor of Maternal and Fetal Health, Director of the Tommy's Centre for Maternal and Fetal Health, University of Edinburgh MRC Centre for Reproductive Health Queen's Medical Research Institute; Philip Owen, Consultant Obstetrician and Gynaecologist, North Glasgow NHS Trust; Jane Plumb, Lay member; Farrah Pradhan, Lay member; Marianne Rowntree, Midwife, Plymouth Hospitals NHS Trust; Meekai To, Consultant in Fetal Medicine and Obstetrics, Kings College Hospital; Martin Ward Platt, Consultant Paediatrician (neonatal medicine), The Newcastle upon Tyne Hospitals; Louise Weaver-Lowe, Neonatal Nurse, Central Manchester University Hospitals NHS Trust

Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix C in the full guideline appendices (see the "Availability of Companion Documents" field).

Note that the committee chair, members and expert advisers were appointed under NICE's April 2007 Code of Practice for Declaring and Dealing with Conflicts of Interest. NICE published an updated Code of Practice in October 2014 and declarations made after this date were assessed in accordance with the 2014 version.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Preterm labour and birth. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Nov. 447 p. (NICE guideline; no. 25). Available from the National Institute for Health and Care Excellence (NICE) Web site.
- Preterm labour and birth. Appendices A-G. Methods, evidence and recommendations. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Nov. 317 p. (NICE guideline; no. 25). Available from the NICE Web site.
- Preterm labour and birth. Appendix H. Evidence tables. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Nov. 452 p. (NICE guideline; no. 25). Available from the NICE Web site.
- Preterm labour and birth. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2015 Nov. (NICE guideline; no. 25). Available from the NICE Web site.
- Preterm labour and birth. Costing statement. London (UK): National Institute for Health and Care Excellence; 2015 Nov. 6 p. (NICE guideline; no. 25). Available from the NICE Web site.
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Available from the NICE Web site.
- Social value judgements: principles for the development of NICE guidance. London (UK): National Institute for Health and Care Excellence (NICE). 36 p. Available from the NICE Web site.

Patient Resources

The following is available:

- Preterm labour and birth. Information for the public. London (UK): National Institute for Health and Care Excellence; 2015 Nov. 13 p. (NICE guideline; no. 25). Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download in ePub or eBook formats from the NICE Web site.

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